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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,270	07/26/2006	Jean-Francois Pujol	065691-0459	8373

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FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
CRUZ, KATHRIEN ANN	
ART UNIT	PAPER NUMBER
1628	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,270	PUJOL ET AL.	
	Examiner	Art Unit	
	KATHRIEN CRUZ	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,16 and 18-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,16 and 18-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/02/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 12-28 are pending.

Claims 12,16 and 18-28 are examined herewith.

Priority

This application claims priority of PCT/FR05/00178 dated 01/27/2005.

Action Summary

Claims 12-16 and 18-22 are rejected under 35 U.S.C. 112, first paragraph is withdrawn.

Claims 12 and18-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Aktogu et al (U.S. Patent 5,034,396) is withdrawn due to applicant's amendment of claims.

Claims 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aktogu et al (U.S. Patent 5,034,396) as applied to claims 12 and 18-22 above, and further in view of Pickar et al (U.S. Patent 5,663,167) is withdrawn due to applicant's amendment of claims.

However, upon further consideration, a new rejection is made below.

Response to Arguments

Applicants argue that the PTO has failed to establish a prima face case of obviousness. This argument has been fully considered but has not been found persuasive. Aktogu et al teaches a method of treating depression in a warm-blodded animals with the administration of formula I which is (3α, 14β) 14, 15-dihydro 20,21-dinoreburnamenin-14-ol and (14β, 16α) 14, 15-dihydro 20, 21-dinoreburnamenin-14-ol (claims 1-3).). Pickar teaches that the addition of an alpha$_2$ receptor antagonist are useful in the treatment of patents suffering from serious psychotic mental illness who have proven resistant to treatments with known antipsychotic neuroleptics alone (column 2, lines 40-43). Andres teaches that blockade of α_2-adrenoceptors in the brain inhibits the negative feed back NE exerts on its own synthesis, neuronal firing and releases, resulting in enhanced NEergic neurotransmission. α_2-adrenoceptors blockade also increases extracellular dopamine, acetylcholine and SER levels in vivo in the rat and human. Furthermore, combination therapy of depressive patients with drugs with an α_2-adrenoceptors antagonistic component in addition of an SSRI, have repeatedly shown increased efficacy and effectiveness on treatment resistant patients (page 2720, left column, second paragraph). It would have been obvious to one of ordinary skills in the art to employ the administration of formula I which is (3α, 14β) 14, 15-dihydro 20,21-dinoreburnamenin-14-ol and (14β, 16α) 14, 15-dihydro 20, 21-dinoreburnamenin-14-ol to a subject is partially or totally resistant to classical anti-depressants. One would have been motivated to treat a subject is partially or totally resistant to classical anti-depressants because Pickar teaches that alpha$_2$ receptor

antagonist are useful in the treatment of mental illness (e.g. bipolar, schizophrenia) to subjects who are drug resistant to known antipsychotic neuroleptics alone. Additionally, it is known in the art that α_2-adrenoceptors antagonistic component in addition of an SSRI, have repeatedly shown increased efficacy and effectiveness on treatment resistant patients as taught by Andres. It would have been obvious to one of ordinary skills to employ alpha$_2$ receptor antagonist in combination or singularly with known antidepressants since it is taught in the prior art that alpha$_2$ receptor antagonist are useful in the treatment of drug resistant subject with a reasonable expectation of success. Therefore, the rejection under 35 U.S.C 103(a) is deemed proper.

Applicants argue that there is no medicament available for treating "treatment resistant depression". This argument has been fully considered but has not been found persuasive. Aktogu et al teaches a method of treating depression in a warm-blodded animals with the administration of formula I which is (3α, 14β) 14, 15-dihydro 20,21-dinoreburnamenin-14-ol and (14β, 16α) 14, 15-dihydro 20, 21-dinoreburnamenin-14-ol (claims 1-3).). Pickar teaches that the addition of an alpha$_2$ receptor antagonist are useful in the treatment of patents suffering from serious psychotic mental illness who have proven resistant to treatments with known antipsychotic neuroleptics alone (column 2, lines 40-43). Andres teaches that blockade of α_2-adrenoceptors in the brain inhibits the negative feed back NE exerts on its own synthesis, neuronal firing and releases, resulting in enhanced NEergic neurotransmission. α_2-adrenoceptors blockade also increases extracellular dopamine, acetylcholine and SER levels in vivo in the rat and human. Furthermore, combination therapy of depressive patients with

drugs with an α_2-adrenoceptors antagonistic component in addition of an SSRI, have repeatedly shown increased efficacy and effectiveness on treatment resistant patients (page 2720, left column, second paragraph). It would have been obvious to one of ordinary skills in the art to employ the administration of formula I which is (3α, 14β) 14, 15-dihydro 20,21-dinoreburnamenin-14-ol and (14β, 16α) 14, 15-dihydro 20, 21-dinoreburnamenin-14-ol to a subject is partially or totally resistant to classical anti-depressants. One would have been motivated to treat a subject is partially or totally resistant to classical anti-depressants because Pickar teaches that alpha$_2$ receptor antagonist are useful in the treatment of mental illness (e.g. bipolar, schizophrenia) to subjects who are drug resistant to known antipsychotic neuroleptics alone. Additionally, it is known in the art that α_2-adrenoceptors antagonistic component in addition of an SSRI, have repeatedly shown increased efficacy and effectiveness on treatment resistant patients as taught by Andres. It would have been obvious to one of ordinary skills to employ alpha$_2$ receptor antagonist in combination or singularly with known antidepressants since it is taught in the prior art that alpha$_2$ receptor antagonist are useful in the treatment of drug resistant subject with a reasonable expectation of success. Therefore, the rejection under 35 U.S.C 103(a) is deemed proper.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 23-28 rely upon support data for the wake sleep cycle disorder not treatment resistant depression. Therefore, the instant claims 23-28 do not have support for treatment resistant depression.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 12, 16, 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aktogu et al (U.S. Patent 5,034,396) Pickar et al (U.S. Patent 5,663,167) both are of record and in further view of Andres (Synthes of 3a,4-Dihydro-3H[1]benzophyrano[4,3-c]isoxazoles, Displaying Combines 5-HT Uptake Inhibiting and α_2-adrenoceptors Antagonistic Activites: A Novel Series of Potential Antidepressants, Boorganic & Medicinal Chemistry Letters 13 (2003) pages 2719-2725).

Aktogu et al teaches a method of treating depression in a warm-blodded animals with the administration of formula I which is (3α, 14β) 14, 15-dihydro 20,21-dinoreburnamenin-14-ol and (14β, 16α) 14, 15-dihydro 20, 21-dinoreburnamenin-14-ol (claims 1-3). Aktougu et al teaches that the above mentioned compounds may be orally administered, rectally, topically or parenteraly and the usual daily dose is 0.133 to 2.66 mg/kg (column 3, lines 66-68). Examiner notes that the average patient is presumed approximately 70 kg, the dosage range would be 9.31mg to 186.2 mg. Aktogu teaches that the compositions of formula I have an important affinity for alpha$_2$ receptor between the two enantiomers of each racemic product (column 3, lines 48-51).

Aktogu does not expressly teach that the subject is partially or totally resistant to classical anti-depressants. Aktogu does not expressly teach bipolar as the form of depression.

Pickar teaches that alpha$_2$ receptor antagonist are useful in the treatment of bipolar disorders (abstract, column 3, lines 5-15 and claim 13). Pickar teaches the

dosage of alpha$_2$ receptor antagonist are administered in the amount of 60 to 120 mg/day (claim 15). Pickar teaches that the addition of an alpha$_2$ receptor antagonist are useful in the treatment of patents suffering from serious psychotic mental illness who have proven resistant to treatments with known antipsychotic neuroleptics alone (column 2, lines 40-43).

Andres teaches that blockade of α_2-adrenoceptors in the brain inhibits the negative feed back NE exerts on its own synthesis, neuronal firing and releases, resulting in enhanced NEergic neurotransmission. α_2-adrenoceptors blockade also increases extracellular dopamine, acetylcholine and SER levels in vivo in the rat and human. Furthermore, combination therapy of depressive patients with drugs with an α_2-adrenoceptors antagonistic component in addition of an SSRI, have repeatedly shown increased efficacy and effectiveness on treatment resistant patients (page 2720, left column, second paragraph).

It would have been obvious to one of ordinary skills in the art to employ the administration of formula I which is (3α, 14β) 14, 15-dihydro 20,21-dinoreburnamenin-14-ol and (14β, 16α) 14, 15-dihydro 20, 21-dinoreburnamenin-14-ol to a subject is partially or totally resistant to classical anti-depressants. One would have been motivated to treat a subject is partially or totally resistant to classical anti-depressants because Pickar teaches that alpha$_2$ receptor antagonist are useful in the treatment of mental illness (e.g. bipolar, schizophrenia) to subjects who are drug resistant to known antipsychotic neuroleptics alone. Additionally, it is known in the art that α_2-adrenoceptors antagonistic component in addition of an SSRI, have repeatedly shown

increased efficacy and effectiveness on treatment resistant patients as taught by Andres. It would have been obvious to one of ordinary skills to employ alpha$_2$ receptor antagonist in combination or singularly with known antidepressants since it is taught in the prior art that alpha$_2$ receptor antagonist are useful in the treatment of drug resistant subject with a reasonable expectation of success.

Examiner's Note: formula I which is (3α, 14β) 14, 15-dihydro 20,21-dinoreburnamenin-14-ol and (14β, 16α) 14, 15-dihydro 20, 21-dinoreburnamenin-14-ol is also known by RU24722 and Vindeburnol.

Claims 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aktogu et al (U.S. Patent 5,034,396) Pickar et al (U.S. Patent 5,663,167) both are of record and in further view of Andres (Synthes of 3a,4-Dihydro-3H[1]benzophyrano[4,3-c]isoxazoles, Displaying Combines 5-HT Uptake Inhibiting and α_2-adrenoceptors Antagonistic Activites: A Novel Series of Potential Antidepressants, Boorganic & Medicinal Chemistry Letters 13 (2003) pages 2719-2725) as applied to claims 12, 16 and 18-22 above, and further in view of Bourde (Lond Term effect of RU24722 ON Tyrosine Hydroxylase in the rat Locus Coeruleus: differential Effects of Two Enantiomeric Forms, Neurochem Int. Vol 23, No 6 (1003) Pages 567-574).

Aktogu, Pickar and Andres as cited above.

None of the above references expressly teach increase the number of the noradrenergic and hypocretin neurons. Nor does the prior cited art teach the increase

of the density of noradrenalin fibers in the prefrontal cortex or an increased REM sleep after sleep depravation.

Bourde teaches the administration of RU 24722 (instant claim formula 1) from the 16α to the 3α configuration induces a significant 3-fold decrease of the optimal efficiency of the molecule in inducing long term tyrosine hydroxylase (herein after TH) changes in the Locus Coeruleus (herein after LC). Moreover, the similar long term effect on the TH protein of the molecule was obtained after treatment by the molecule obtaine by dehycration of RU24722 at the level of the carbon NO 14 hydroxyl group. It strongly suggests that the hydroxyl moietie does not interfere with the capacity of RU24722 of induce TH protein (page 571, right column, first paragraph). Bourde teaches that RU 24722 induce after a single injection long term increase in TH in totally inhibited LC neurons (page 572, right column, second paragraph). Bourde teaches that various studies have demonstrated the efficiency of α_2 antagonist to activate LC neurons and large number of α_2 adrenoceptors are present in the LC (page 572, left column, second paragraph). Bourde teaches RU24722, in a single dose, activates LC noradrenergic neurons (page 572, right column, first paragraph).

It would have been obvious to one of ordinary skills in the art at the time of the invention was made that the administration of RU24722 for treatment resistant depression would also result in the increase of the number of the noradrenergic and hypocretin neurons, the increase of the density of noradrenalin fibers in the prefrontal cortex and an increased REM sleep after sleep depravation with the same administration of RU24722 to the same population for the same disorder. Further more,

it is known in the art that in various studies have demonstrated the efficiency of α_2 antagonist to activate LC neurons and large numbers of α2 adrenoceptors are present in the LC as taught by Bourde. Bourde teaches that RU 24722 induces after a single injection long term increase in TH in totally inhibited LC neurons. Bourde teaches RU24722, in a single dose, activates LC noradrenergic neurons. Therefore, it is obvious that with the administration of RU24722 for treatment resistant depression would also result in the increase of the number of the noradrenergic and hypocretin neurons, the increase of the density of noradrenalin fibers in the prefrontal cortex and an increased REM sleep after sleep depravation with the same administration of RU24722 to the same population for the same disorder.

For these reasons, the claimed subject matter is deemed to fail to be patentably distinguishable over the state of the art as represented by the cited reference. The claims are therefore, properly rejected under 35 U.S.C. 103.In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Claims 12, 16 and 18-28 are rejected.

No claims are allowed.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KATHRIEN CRUZ whose telephone number is (571)270-5238. The examiner can normally be reached on Mon - Thurs 7:00am - 5:00pm with every Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KATHRIEN CRUZ/
Examiner, Art Unit 1628

/San-ming Hui/
Primary Examiner, Art Unit 1628